A STUDY OF DISPERSION OF AN INDICATOR IN THE CIRCULATION*

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Although many investigators have studied the dispersion of an indicator as it traverses a particular vessel or even a certain organ, no attempt has been made to date to analyze the dispersion of an indicator that occurs in one complete transit around the circulation.[1] In the present studies, experiments were performed to allow quantitative evaluation of this phenomenon in anesthetized dogs and in resting and exercising humans. From these observations, a mathematical model has been derived to represent quantitatively the dispersion of an indicator at any time after injection into the bloodstream. This model of mixing in the circulation uses the principle of convolution or superposition to synthesize the mixed-venous indicator-dilution curve when the fraction of cardiac output traversing each organ and the mathematical function describing the distribution of indicator transit times through that organ are known. Conversely, when the distribution function of each organ and the time course of indicator concentration in the mixed venous blood are known, the fraction of the cardiac output traversing each organ can be determined.

Theory

Fundamentally, mixing of the circulating blood with an indicator injected into the circulation is due to the fact that not all the indicator traverses the circulation in the same time. This mixing may be divided into four processes (FIGURE 1). First, mixing results from the difference of flow velocity in a cross section of a single artery or vein, such as is known to occur in those segments of the circulation where there is laminar flow.[2,3] Second, in passing through the heart, the blood that enters during each diastole is mixed with the residual blood from the previous systole. Process two could be lumped with process one, since it represents a difference in velocity of dye particles traversing a single channel. A third type of mixing is due to

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the difference of path lengths through a given organ. Even more effective in producing dispersion, however, is the fourth mixing process, which arises from a difference in path lengths (and thus passage times) in different organs. For instance, the transit time through the legs at rest is much longer than through the kidneys. Insight into the part of each of these mixing processes in the over-all mixing effect could be gained by examining the theoretical time course of indicator to be expected following a unit impulse

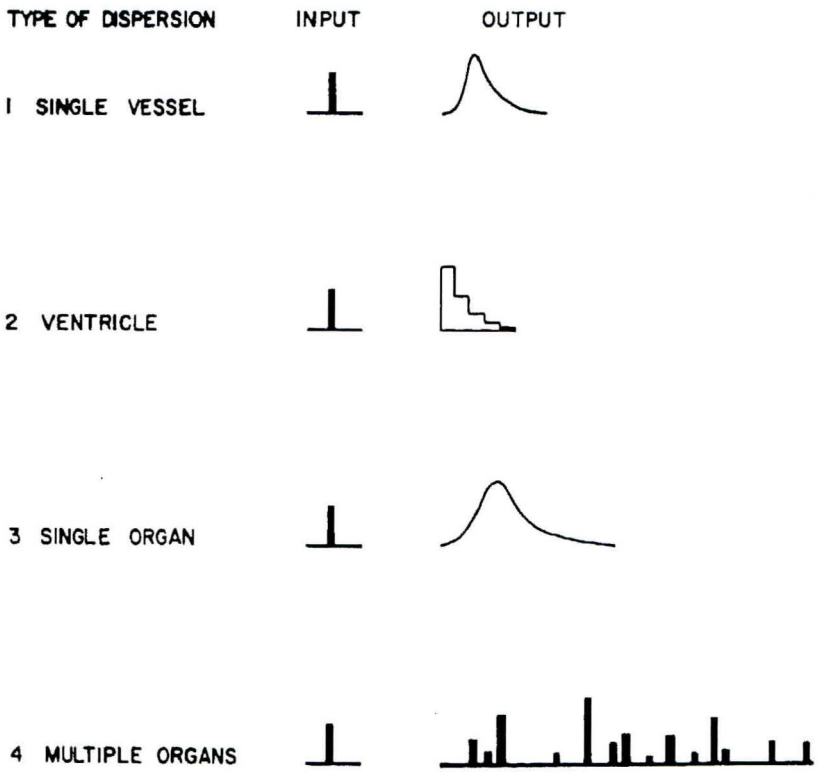


FIGURE 1. Schematic representations of time course of indicator concentration to be expected from each process of dispersion acting on a single impulse injection.

injection into a system if only one of these processes were operating at the time.

As represented in FIGURE 1, sudden single injection into a single tube produces a downstream time course of indicator resembling a skewed normal distribution curve.[4] This distribution $h(t)$ is of the form shown in:

$$h(t) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\frac{(t-t_1)^2}{\sigma^2}} - Th'(t) \qquad (1)$$

where $h(t)$ is the fraction of the dye particles having a particular transit time t, σ is the standard deviation *(sigma)*, t_1 is the mean time of the normal distribution and is equal to the mean transit time of the skewed distribution minus T, the time constant *(tau)* of the lag term. The term $h'(t)$ is the derivative of $h(t)$ with respect to time.

Following a unit impulse injection, process two (mixing in a ventricle) would result in an exponential decay with a step length equal to the duration of the heart cycle and a time constant for the exponential decay equal to $1.0/\log e\ (1.0 + k)$ where k is the ratio of stroke volume to residual volume, as shown in:

$$Cv(I+1) = \frac{(Ca(I))(S.V.) + (Cv(I))(R.V.)}{S.V. + R.V.} \qquad (2)$$

$Ca(I)$ is the concentration of dye entering the ventricle from the atrium on any diastole designated I. $Cv(I)$ is the concentration of dye leaving the ventricle on systole I. $R.V.$ represents residual volume and $S.V.$ means stroke volume. $Cv(I+1)$ is the concentration of dye leaving the ventricle on systole $(I+1)$. This phenomenon has been thoroughly studied both experimentally and theoretically.[5,8]

A unit impulse injection into an artery of a single organ demonstrates the response expected from process three. Like the effect of process one, this result can be described adequately by a skewed normal distribution curve. In general, the parameters of the curve for process three are somewhat larger than those for process one. The curve of process three is smooth since there are so many pathways through an organ that the transit times through them fuse into a continuous distribution.

The distribution of transit times resulting from process four—that is, the difference in transit times through various organs—might be that illustrated in FIGURE 1 if this process could be examined separately from one, two, and three, which obviously occur simultaneously with it *in vivo*. Since there is a finite number of organ systems, discrete peaks within the distribution curve would be expected if the dispersion that occurs within every organ and within every tube conveying blood to or from an organ could be eliminated. It is obvious that supervention of processes one, two, and three on the effect of process four tends to smooth out this distribution curve. However, there is no *a priori* reason why one would expect this distribution to follow a skewed normal distribution as did processes one and three.

Experiments on Dispersion of Dye

In this study experiments were performed to produce data which would permit evaluation of the dispersion of an indicator across segments of the circulation as well as around the complete circulation. Five mongrel dogs, anesthetized with morphine (5 mg./kg.) supplemented with pentobarbital,

were studied thus during control states and during constant infusion of adenosine triphosphate (ATP) into the descending aorta; and four normal human subjects were studied at rest and during exercise in a supine position. In the dogs a No. 6 radiopaque Teflon catheter for injection of dye was passed by way of the external jugular vein and via a transseptal puncture into the left atrium. After injection of dye into some dogs, blood was sampled simultaneously from the pulmonary-artery trunk (PAT) and from the aortic root through No. 5 catheters (length: 55 cm., lumen volume: 0.50 ml.) by Harvard Constant Rate sampling devices set at a constant rate of 24.5 ml./min. Alternatively, injection was made through a similar catheter whose tip lay in the superior vena cava (SVC).

In other dog experiments, dye-dilution curves were recorded simultaneously from a systemic artery, the pulmonary artery, and a third site whose location was changed during the experiment—SVC, hepatic vein, renal vein, inferior vena cava (IVC) below the renal vein, and iliac vein. The injections of dye were into the SVC or left atrium in all of these experiments but one. In that one, injections were made into the aorta at the level of the diaphragm (above the renal arteries) and just above the iliac bifurcation (below the renal arteries); and sampling on the venous side in these instances was from the pulmonary artery and iliac vein.

In the experiments on normal humans, injections were made into the SVC and samples were obtained simultaneously from the left radial artery, the pulmonary artery, and one of the following sites: iliac vein, IVC at the level of the renal vein, or SVC. In these experiments the pulmonary-artery sampling system and the system used for sampling from the other sites in the venous side of the circulation were the same, utilizing a No. 7 catheter (length: 125 cm., lumen volume: 27 ml.) attached to a Harvard Constant Rate device which sampled at 24.5 ml./min. Exercise was performed in the supine position by pedaling a bicycle ergometer at a prescribed rate which the subject could observe on a speedometer.

Analytical technics. Throughout the analysis to follow, the dispersion of indicator in the circulation is assumed to satisfy the basic conditions of linearity and stationarity during the first passage of dye through the central circulation.[3,6,7] Recording and normalizing of the time course of indicator concentration at a pulmonary-artery sampling site following injection into the SVC, within one minute of each other, of single, half, and double quantities of dye, demonstrated the presence of linearity over the time course of the first and second circulation of dye past the pulmonary-artery recording site. Stationarity relative to the three dye curves was not present during the second circulation of dye past the pulmonary-artery sampling site. Apparently, this is due to the lability of the parameters which describe the systemic circulation.[9]

If dye concentration is measured as a function of time at a point downstream from an injection site and if $h(t)$ (Equation 1), the unit impulse

response, is the true distribution of transit times between these two points in the system, the convolution of the time concentration curve recorded at the first site with *h(t)* (superposition principle) will yield the time course of dye concentration at the second downstream sampling site.[3,7,10] A digital computer program has been written to find the optimal parameters of the distribution function *h(t)* required for best predicting a downstream indicator-dilution curve from the basis of an upstream curve. This program involves an iterative solution of the integral equation with successive approximations to the optimal solution. The program accomplishes this by successively changing *sigma*, *tau*, and t_1 (Equation 1) after each solution on the basis of the least-square differences between the theoretical curve and the recorded downstream curve (coefficient of variation).

Results

In all original oscillographic recordings of dye-dilution curves, increasing dye concentration is shown as a downward deflection. For computer solutions, on the other hand, the plot coordinates are positive for increase of time and of dye concentration.

Upstream (pulmonary-artery) and downstream (aortic-root) time courses of indicator concentration following injection of indocyanine green (Cardiogreen) dye into the SVC of an anesthetized dog during a control state appear in FIGURE 2*a*, and comparable curves recorded during infusion of ATP into the descending aorta are in FIGURE 2*b*. The pulmonary-artery curves represent the input; the aortic curves represent the output from the pulmonary circulation and left heart.

With the computer program described above, solutions to Equation 1 were obtained *(h(t))* and convolved with the input curve (pulmonary-artery). The result of this convolution is a prediction of the aortic curve. The computer solution converges on the parameters of *h(t)* which best describe the dispersion of indicator between these two sites by reestimating the parameters *(sigma, tau,* and t_1*)* on the basis of a comparison of the predicted and recorded aortic curves after each solution until this difference (coefficient of variation) falls below a prescribed tolerance.

If the sampling systems for the sites upstream (pulmonary-artery) and downstream (aorta) have the same dynamic response, no correction for "smearing" of the curves by the sampling systems need be made in order that *h(t)* be interpreted as a true descriptor of the intravascular mixing between these points. This is expressed in:

$$h_s = \frac{O_s}{I_s} = \frac{g_s O_s}{g_s I_s} \tag{3}$$

where h_s is the Laplace transform of *h(t)*, and O_s, I_s, and g_s are the

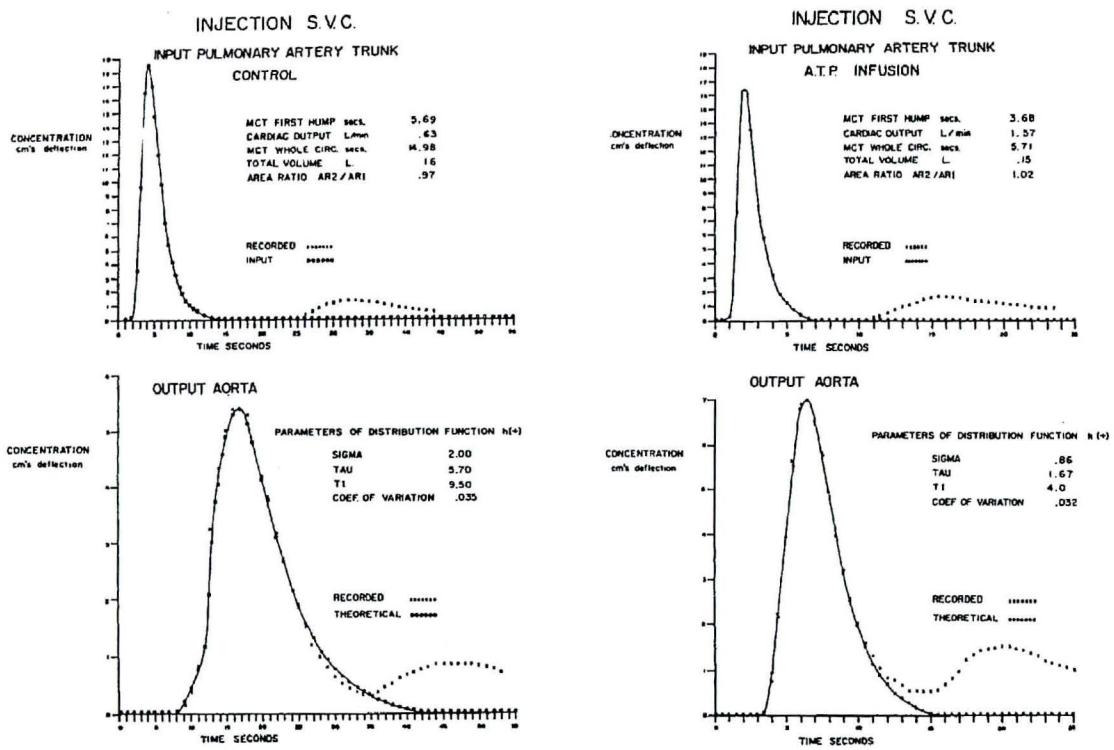


FIGURE 2. Comparisons of curves for circulation of indicator from SVC as recorded from aortic root of dog *(lower panels)* with theoretical aortic curves obtained by convolving pulmonary-artery curve *(upper panels)* with *h(t)* using parameters shown. *(a, left)* During control state. *(b, right)* During infusion of ATP into descending aorta.

transforms of the output and input indicator-concentration curves and of the catheter sampling systems, respectively.

This example illustrates the method used in solving for the distribution function of an organ system in the circulation. The ratio (AR2/AR1) of the area of the output (aortic) curve to the input (PAT) curve is essentially unity both before and during infusion of ATP, indicating that the same amount of dye passed each recording site during the first circulation of dye.

The volume of blood between the two sampling sites may be calculated by the Stewart principle as the product of cardiac output (C.O.) and the sum of two of the parameters of $h(t)$, T, and t_1:

$$Volume = C.O.\ (T + t_1) \tag{4}$$

As shown in FIGURE 2, the parameters of the distribution function relating the input and output deflections during infusion of ATP differ from those during the control state. Although the mean circulation time was decreased and the cardiac output was increased, the blood volume of the pulmonary circulation and left heart did not change significantly in this dog, despite the marked peripheral vasodilatation and increase of cardiac output produced by the ATP.

If the first concentration peak (hump) of an indicator-dilution curve is extrapolated to zero concentration to eliminate second-circulated dye,[11] this extrapolated (primary circulation) curve may then be considered an input function and the curve remaining after subtraction of this primary curve may be considered an output function. The distribution function relating these two curves should describe the distribution of transit times in one complete passage of indicator around the whole circulation and be completely independent of the dynamic characteristics of the sampling system, since both input (first hump) and output (second or recirculation hump) were recorded through the same system. The results of such an analysis of the first and second humps of a dye curve recorded from the pulmonary artery following injection of indocyanine green into the SVC are shown in FIGURE 3.

If the same amount of indicator passed the recording site in the pulmonary artery (FIGURE 3*a*) during inscription of the second (recirculation) hump of the dye curve as passed during inscription of the first (primary circulation) hump, the ratio of the areas under the two humps would be 1:1. However, comparison of the area ratio of the first and second humps of the indicator-dilution curve shows that an amount of dye equal to only 38 per cent of the amount injected traverses the systemic circulation in time to contribute to the second hump of the curve. (Similar results were obtained with Evans blue.) Furthermore, the total blood volume (mean time of the whole circulation multiplied by the cardiac output) is about one-third of that expected for total blood volume. These observations indicate the presence of pathways in the systemic circulation with transit times so long that dye traversing them does not contribute significantly to the second recirculation hump of

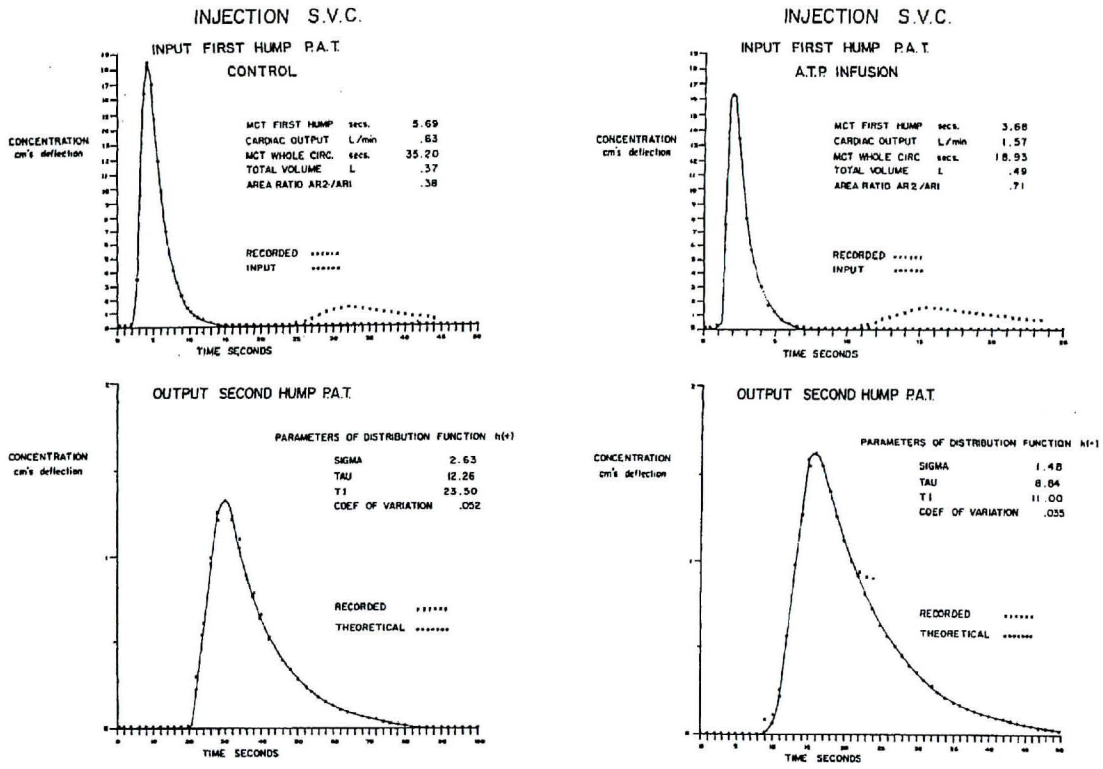


FIGURE 3. Comparisons of secondary (recirculation) deflection (humps) of indicator-dilution curves recorded from dog with recirculation deflections predicted *(lower panels)* by convolving initial (primary circulation) deflections *(upper panels)* with $h(t)$ using parameters shown. (In lower panels, time scale is compressed and concentration scale expanded to facilitate comparison of recorded and theoretical curves.) *(a, left)* During control state. *(b, right)* (Same dog.) During infusion of ATP into descending aorta.

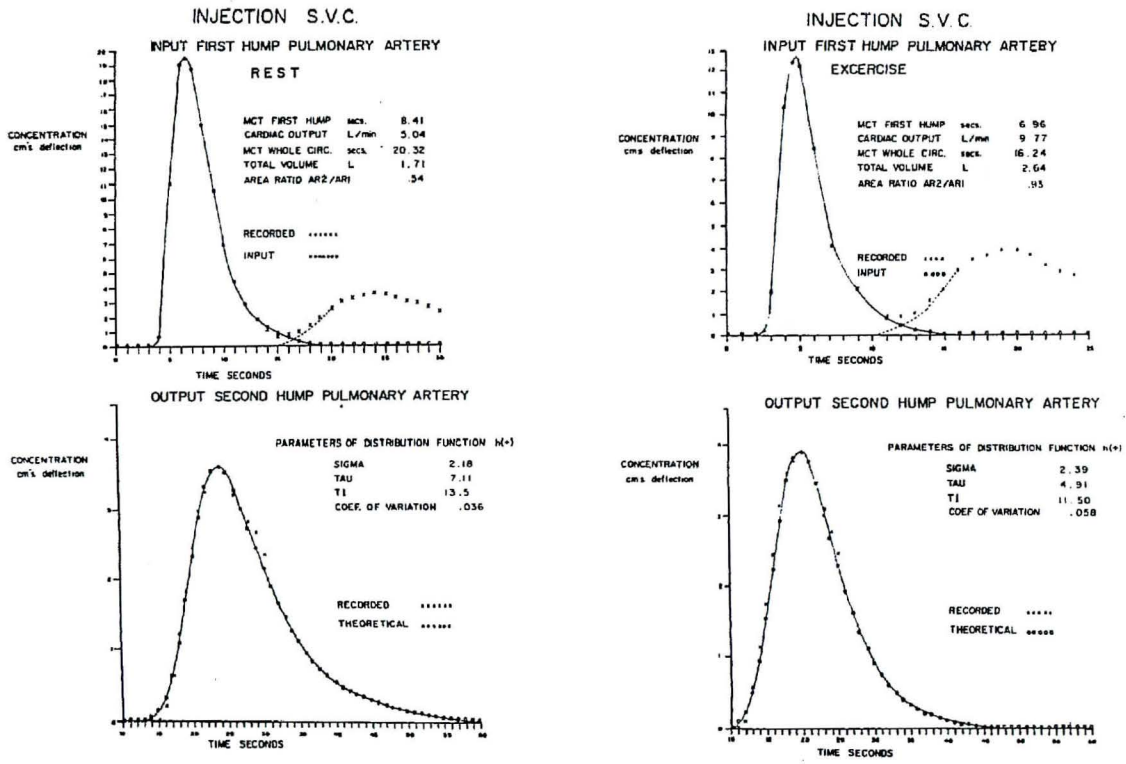


FIGURE 4. Same comparisons as in FIGURE 3 except that curves were obtained from normal conscious human lying supine, at rest *(a, left)* and pedaling an exercycle *(b, right)*. Input function for convolution is pulmonary-artery indicator-dilution curve, after extrapolation to zero by method of Hamilton;[11] output after one complete circuit is remainder of curve after subtraction of input. Dashed lines in upper panels show initial part of output function obtained by subtracting input curve.

a central indicator-dilution curve. A quantitatively similar discrepancy in the area ratio of the second to the first hump is present in the normal human at rest (FIGURE 4*a*).

A result of decreasing the transit time of indicator through the lower extremities by intra-aortic injection of ATP in a dog (FIGURE 3*b*) and by bicycle exercise in the supine position in man (FIGURE 4*b*) is to increase the area ratio toward 1.0. However, even when the area ratio becomes 1.0 (or more) in the presence of increased cardiac output and increased peripheral vasodilatation, the calculated total blood volume is still only about half that expected for subjects of this size. It seems apparent, then, that during conditions of increased cardiac output and increased peripheral vasodilatation, dye traversing some short or fast pathways contributes more than once to the second hump of an indicator-dilution curve while dye traversing other much longer or slower pathways does not arrive in time to contribute at all to this second hump. These findings confirm the presence of slow and fast pathways in the systemic circulation as originally studied by Stewart.[12-14]

Experiments on Transit Times

The results just presented suggested a series of experiments on dogs and humans designed to determine the distribution of transit times through various organs perfused by the systemic circulation. The time course of indicator concentration was measured simultaneously in pulmonary-artery blood and in blood from one of several sites in the venous system. In FIGURE 5 are shown indicator-dilution curves recorded from the sites indicated following injection of indocyanine green into the left atrium or aorta. Note that the pulmonary-artery curve is past its maximal deflection before any dye appears at the iliac or hepatic veins or SVC, whereas the renal-vein curve appears between the femoral-artery and pulmonary-artery curves in respect to time. In the two frames on the right, where the sites of injection were in the aorta above and below the origin of the renal arteries, the venous sampling sites were in the pulmonary artery and iliac vein. These curves show that, when indicator is injected into the aorta below the level of the renal artery in an amount sufficient to produce a large deflection at the femoral artery, the deflection in the pulmonary-artery curve is hardly detectable.

The indicator-dilution curves shown in FIGURE 6 were obtained from a normal human subject. Indocyanine green was injected into the SVC and sampled from the pulmonary artery and from various sites in the venous circulation. The three sets of curves in the left panel were obtained during rest and those in the right panel during exercise as described. Both with rest and with exercise, the concentration curve at the renal vein was slightly ahead of the second (systemic recirculation) hump in the pulmonary-artery curve. In contrast to this, the dye appeared only very late in the iliac vein

at rest; but during exercise the appearance at the iliac vein corresponded very closely to the second hump in the pulmonary-artery curve. With rest and with exercise, the appearance at the SVC in this subject was slightly later than the second hump on the pulmonary-artery curve. (The initial deflection on the SVC curve recorded during exercise is an artifact due to

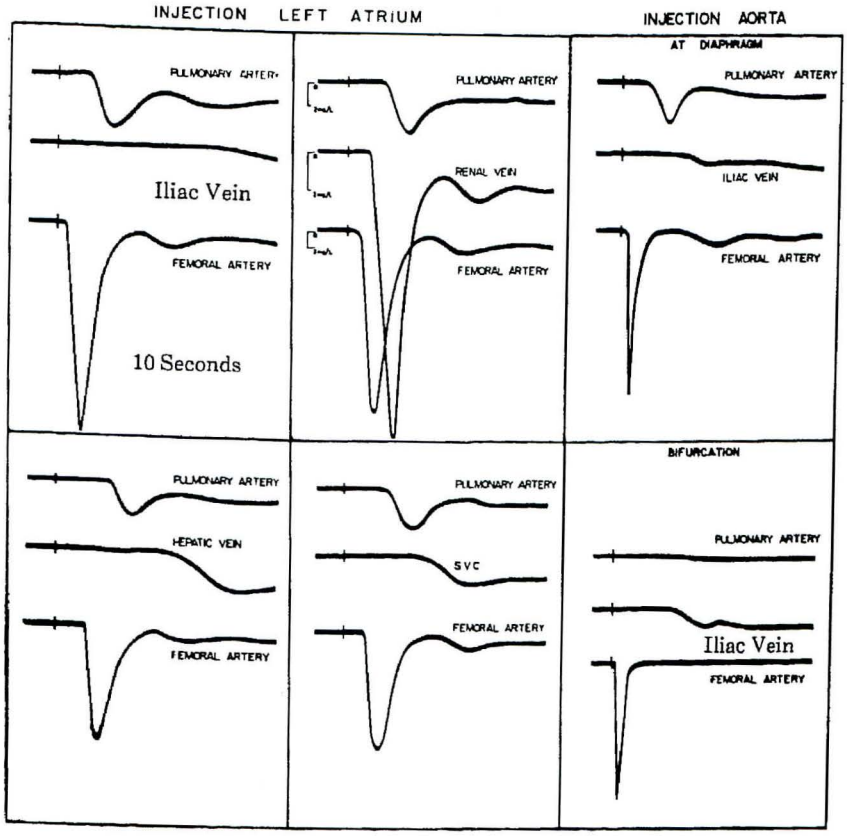


FIGURE 5. Each frame shows three indicator-dilution curves recorded simultaneously from stated sites in anesthetized dog after injection of indocyanine green into left atrium or aorta. The doses of dye used were 4.7 mg. and 2.7 mg. in the left atrial injections shown in the upper and lower panels, respectively, as compared to 1.75 and 0.40 mg. for the aortic injections above and below the renal veins, respectively.

immediate sampling of the injection. In this circumstance, the second deflection represents the first circulation of dye past the SVC sampling catheter.) In some subjects the SVC curve was even later in developing. Although exercise was confined mainly to the subject's legs, other parts of his body contributed to the exertion in varying amounts.

It is apparent from these observations (FIGURES 5 and 6) that the initial hump on the pulmonary-artery curve of a resting subject after left atrial injection is due largely to dye that has traversed the renal and coronary circulations. In these experiments, coronary-sinus blood was not sampled; but the mean transit time through the coronary circulation is of the same order as that through the renal circulation.[15]

Mathematical Model

Once experiments have been performed to measure the time course of indicator in the aorta and in each of the major venous pathways draining

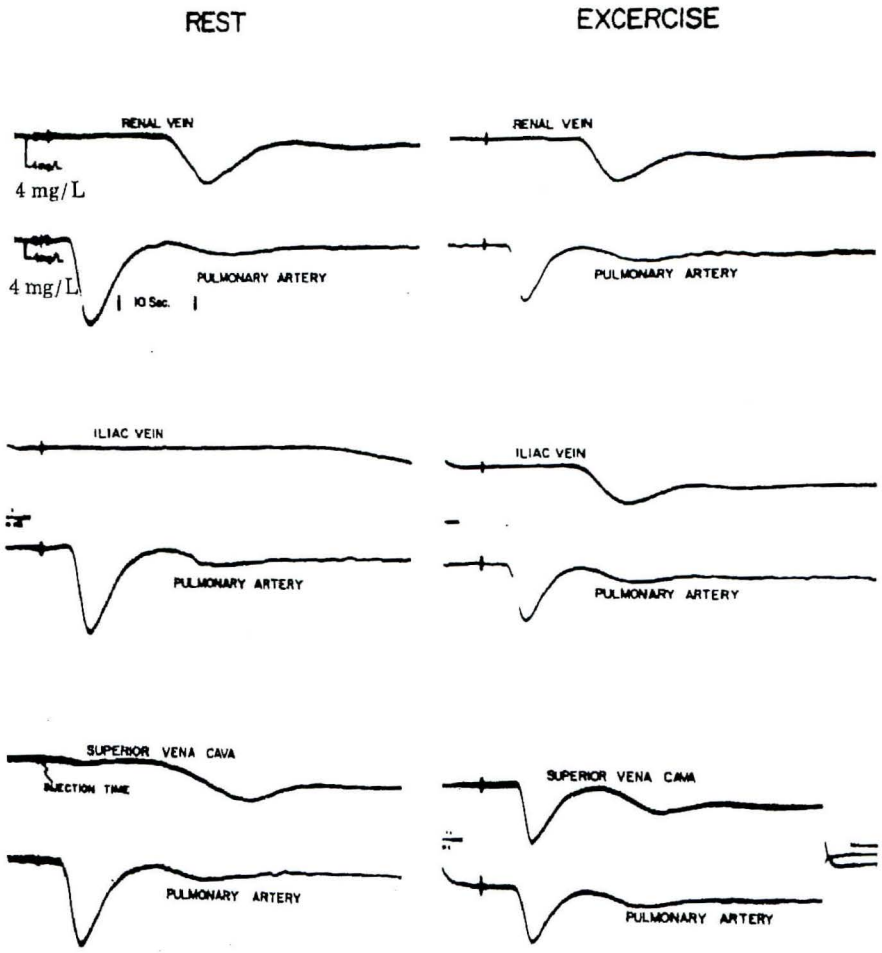
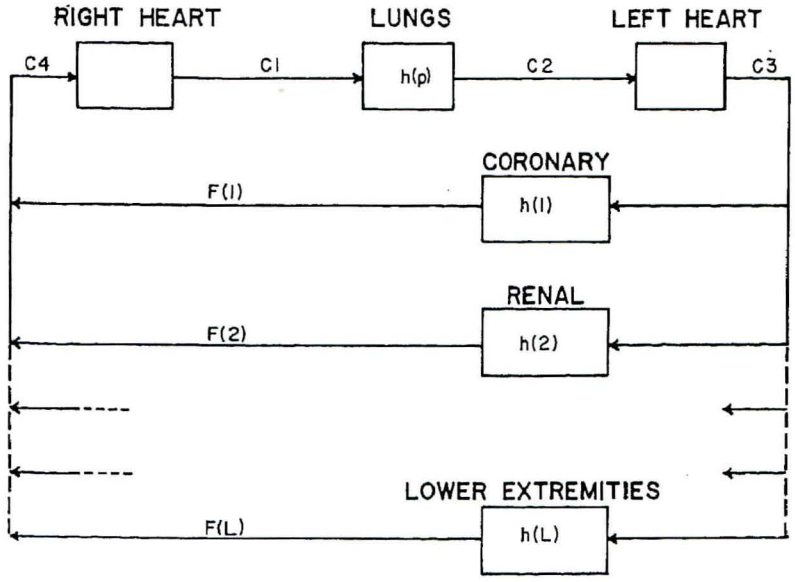


FIGURE 6. Six pairs of indicator-dilution curves recorded from stated sites in normal human subject following injection of indocyanine green into SVC. The dose of dye used was 7.78 mg. for each injection.



$$C4\ (t) = \sum_{I=1}^{I=L} F\ (I) \sum_{J=1}^{J_{(t)}} \sum_{K=1}^{K_{(t)}} C3\ (J)\ H\ (I, J+K-1)\Delta D$$

FIGURE 7. Schematic representation of the mathematical model of mixing in the circulation, and representation of numerical approximation to Equation 5 for computer solution. ΔD (delta D) is set equal to period of heart cycle.

the parallel organ systems, the parameters of the distribution function *(h(t))* of each of these pathways can be calculated by use of a digital computer program as described above. After these distribution functions have been determined, the fraction of the cardiac output traversing each of these pathways may then be estimated with application of a mathematical model. FIGURE 7 shows a schematic representation of this model and the numerical approximation of:

$$C_4(t) = F_1 \int_0^t C_3(\lambda)\, h_1(t-\lambda)\, d\lambda + F_2 \int_0^t C_3(\lambda)\, h_2(t-\lambda)\, d\lambda +$$

$$\cdots + F_L \int_0^t C_3(\lambda)\, h_L(t-\lambda)\, d\lambda \qquad (5)$$

used in solving the model equations on a digital computer. To start the simulation, the indicator concentration at one point in the circulation—for instance, the right heart—is set to a positive value and initial concentration values elsewhere are set to zero. Then the time course of indicator leaving

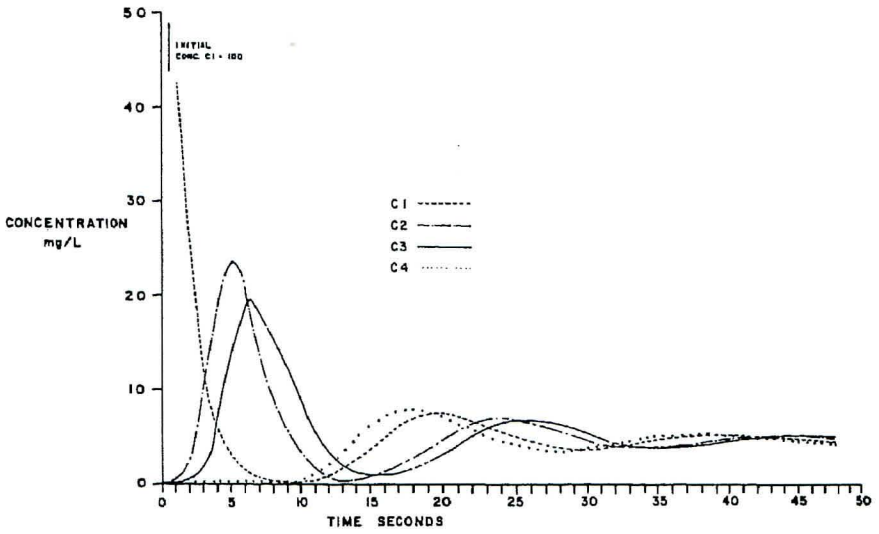


FIGURE 8. Mixing model solution. Time course of indicator concentration in pulmonary artery (C_1), left atrium (C_2), aorta (C_3), and right atrium (C_4) predicted by mathematical model following a sudden single injection into right ventricle.

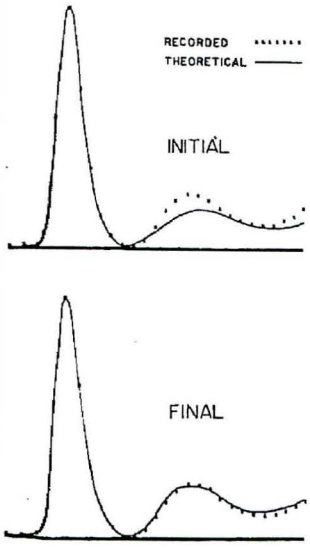
the right heart is described by Equation 2, assuming complete ventricular mixing. This curve is the input C_1 to the pulmonary circulation. C_1 (t) is convolved with the distribution function $h(P)$ across the lungs to give the input concentration C_2 at the left ventricle. C_3 (t) is the time course of indicator concentration in blood entering the aorta from the left ventricle. The indicator next enters a series of parallel pathways through the various organ systems of the systemic circulation. The sum of the output curves from these paths determines C_4. This summation and convolution is shown in Equation 5 where the input C_3 is convolved with each of the distribution functions for the L pathways and each is multiplied by its appropriate flow fraction before summing to obtain C_4. C_4 (t) then is the input to the right heart. The model is simulated on a general-purpose digital computer.

The behavior of the model is determined by the following parameters: stroke volume, heart rate, residual volume of each ventricle, fraction of total cardiac output traversing each parallel pathway through the systemic circuit, and distribution function describing the dispersion process through each of these pathways and through the lungs. FIGURE 8 is a plot of C_1, C_2, C_3, and C_4 from a solution by theoretical model. This simulation was begun with arbitrary initial-flow fractions and with initial concentrations of dye set at 100 mg./l. for C_1 and zero for C_2, C_3, and C_4.

Since mixing which occurs in the ventricle following a sudden single injection at that site is not always complete, and since processes two and three can be lumped with process one (FIGURE 1), mixing in the central vascular

bed (pulmonary artery, lungs, pulmonary veins, and left heart) can be described by the parameters of a single skewed normal distribution (FIGURE 2). The validity of lumping two or more functions of the form $h(t)$ as another function of the same form but with different parameters can be shown analytically and confirmed by empirical solution by the computer.[3,7,16]

The solution (concentration C_3) illustrated in FIGURE 9 was obtained by means of the mathematical model to test the accuracy with which the model could solve for the fraction of cardiac output traversing each major pathway through the systemic circulation if the distribution function through each of these pathways was known. In the curves defined by the separate points, in both upper and lower panels, the flow fractions are those listed under "true value" (the hepatic vein and SVC are lumped because they have essentially identical distribution-function parameters). The solid line in the upper panel is the model solution obtained by setting the initial flow fractions at arbitrary values as shown under "initial" value. In the lower panel is a comparison of the time course of indicator predicted by the model after it has automatically adjusted the flow fractions to obtain the optimal least squares fit to the theoretical recorded curve. A comparison of these final values for the flow fractions with the true values measures the ability of the model to determine the fraction of cardiac output traversing each organ pathway when the distribution function for each component of the system



	RECORDED	THEORETICAL	
	TRUE VALUE	INITIAL	FINAL
CORONARY	.060	.090	.064
RENAL	.200	.050	.199
HEPATIC & S.V.C.	.440	.300	.426
LOWER EXTREMITIES & OTHER SLOW PATHWAYS	.300	.560	.320

FIGURE 9. Comparison of computer solutions for indicator concentration in aorta (C_3) using true values *(points)* and arbitrary values *(solid line, upper panel)* for fraction of cardiac output traversing each organ system. In lower panel is comparison of predicted C_3 after computer program has optimized fit by adjusting flow fractions automatically to those shown in column labeled final.

is known. Thus, this model suggests a basis for measuring the fraction of cardiac output which traverses a particular organ system and provides a general scheme for understanding dispersion in the vascular system.

Summary

An indicator injected into the circulation mixes with the circulating blood by distribution analyzed as four processes. The first three of these processes may be lumped and described by a single skewed normal distribution.

Analysis of the dispersion of an indicator that occurs after one complete transit around the circulation was studied in dogs during control states and during constant infusion of ATP, and in normal humans during rest and during exercise in a supine position. In these experiments the major fast and slow pathways in the systemic circulation were defined. The renal circulation is the principal fast pathway.

The results of these studies led to the formulation of a mathematical model of mixing in the circulation which can describe the dispersion of an indicator at any time after injection into the bloodstream. This model of circulatory mixing is a basis for estimating the fraction of cardiac output which traverses each organ system.

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